

(12)

(21) **2 314 746**

(51) Int. Cl. 7: **A61K 31/44, A61P 19/00,  
A61K 45/06, A61K 9/20**

(22) **01.08.2000**

(30) **60/147,033 US 03.08.1999**

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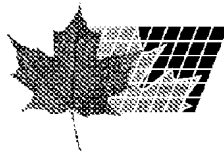
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(54) **UTILISATION DE FLUPIRTINE POUR ATTENUER LES DOULEURS CAUSEES PAR LES MALADIES  
DEGENERATIVES DES ARTICULATIONS CHEZ LES CHIENS ET LES CHATS**

(54) **USE OF FLUPIRTIN FOR AMELIORATION OF PAINS IN THE DEGENERATIVE JOINT DISEASES OF DOGS  
AND CATS**

(57)

The invention relates to a process for ameliorating and preventing inflammatory chronic pain from a degenerative joint disease in household pets as dogs and cats, in which there is administered to a household pet in need therefor a dosage of an analgesically effective amount of flupirtine or a pharmaceutically acceptable salt of flupirtine, optionally together with one or more active ingredients that is an antiinflammatory, an analgesic other than flupirtine, a steroid, a chondroprotector, a TNF receptor, and a plant extract.



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(51) Int.Cl.<sup>7</sup> A61K 31/44, A61K 9/20, A61K 45/06, A61P 19/00  
(30) 1999/08/03 (60/147,033) US  
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DOULEURS CAUSEES PAR LES MALADIES  
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(54) **USE OF FLUPIRTIN FOR AMELIORATION OF PAINS IN THE  
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(57) The invention relates to a process for ameliorating and preventing inflammatory chronic pain from a degenerative joint disease in household pets as dogs and cats, in which there is administered to a household pet in need therefor a dosage of an analgesically effective amount of flupirtine or a pharmaceutically acceptable salt of flupirtine, optionally together with one or more active ingredients that is an antiinflammatory, an analgesic other than flupirtine, a steroid, a chondroprotector, a TNF $\alpha$  receptor, and a plant extract.



Abstract of the disclosure

The invention relates to a process for ameliorating and preventing inflammatory chronic pain from a degenerative joint disease in household pets as dogs and cats, in which there is administered to a household pet in need therefor a dosage of an analgesically effective amount of flupirtine or a pharmaceutically acceptable salt of flupirtine, optionally together with one or more active ingredients that is an antiinflammatory, an analgesic other than flupirtine, a steroid, a chondroprotector, a TNF $\alpha$  receptor, and a plant extract.

Field of invention

5           The present invention relates to a pain treatment process in household pets with flupirtine or its pharmaceutically acceptable salts, as well as for the prevention of chronic pain associated with inflammations in the case of degenerative joint diseases in household pets such as cats and dogs.

Background

10           Degenerative joint diseases are noninflammatory joint diseases which are also referred to as "degenerative joint diseases" (DJD). Degenerative joint diseases occur particularly in dogs, but also in many old cats. Due to the slowly progressing loss of joint cartilage, the mobility of the joint affected is increasingly restricted and this is painful. In dogs and cats, hip  
15 joint dysplasia (growth disorder), kneecap luxation (dislocation of the kneecap or a kneecap incidence) are preliminary stages of these joint diseases. These preliminary stages of the degenerative joint diseases are also painful, even if there is not yet any cartilage damage. In dogs, stretching of the ligaments, ligaments tears (such as crucial ligament tears) or meniscus damage which, on the one hand, is associated with pain and, on the other, favor a renewed  
20 kneecap incidence, also occur frequently in dogs.

          Degenerative joint diseases are basically associated with pain. Occasionally, acute inflammatory episodes occur. In this respect there are differences between man and dog, because these inflammatory reactions proceed in a clearly milder form in dogs. For example, swellings,  
25 which are hardly detectable in dogs, produce very pronounced swellings in man.

          There are further painful diseases in animals, which are partially associated with degenerative changes in the joints. These include, for example, dachshund paralysis or the

Cauda-equina syndrome. The latter is the so-called "horsetail syndrome", which affects predominantly breeds of larger dogs, such as German shepherds. The cause of the pain is the constriction of the spinal canal due to the partial occurrence of cartilaginous spinal disks. Pain, the cause of which can be explained by ligament extension, also occurs if the lumbosacral joint is unstable.

Drugs with different mechanisms of action are used for the treatment of chronic pain. For example, corticosteroids which, because of their mechanism of action, initiate serious side effects in animals, are also employed. Most frequently, however nonsteroidal inflammation-inhibiting drugs, nonsteroidal anti-inflammatories (NSAIDs) and so-called cartilage-protecting (chondro-protective) drugs are used.

The cartilage-protecting substances include polysulfated glycosaminoglycan and the combination of chondroitin and glucosamine. Polysulfated glycosaminoglycan is administered intramuscularly or intra-articularly (directly into the joint). The effectiveness of this mixture is disputed not only in the literature dealing with human medicine, but also in the veterinary science literature (Deal, CL, RW Moskowitz. Nutraceuticals as therapeutic agents in osteoarthritis. – The role of glucosamine, chondroitin sulfate, and collagen hydrolysate. Rheumatic Disease Clinics of North America 25, 379 - 782, 1999; DeHaan, JJ, Goring, RL, BS Beale, Evaluation of polysulfated glycosaminoglycan for the treatment of hip dysplasia in dogs. Vet. Surg. 23, 177 - 181, 1994).

Chondroitin and glucosamine are used orally either as a simple substance (glucosamine) or in combination. Up to the present time, their effectiveness has not been confirmed by controlled clinical studies either in man or even in animals (Leffler, CT, AF Philippi, SG Leffler, JC Mosure, PD Kim, Glucosamine, chondroitin, and magnesium ascorbate for degenerative joint disease of the knee or the low back: A randomized, double-blind, placebo-

controlled pilot study, *Military Medicine* 164, 85 – 91, 1999).

Even if the cartilage-protective substance shows therapeutically advantageous effects under *in vitro* conditions, these effects have not been put to the test under therapeutic conditions (*in vivo*) (Bassler, C, L. Rovati, P. Franchimont. Stimulation of proteoglycan production by glucosamine sulfate in chondrocytes isolated from human osteoarthritic articular cartilage in vitro. *Osteoarthritis & Cartilage* 6, 427 - 434, 1998).

At the present time, there is no medicinal drug, which can prevent the destruction of cartilage. In the future, the destructive processes will be treated with such substances, which causally participate in the pathogenesis of osteoarthrosis and can thus arrest the progress of destruction of the cartilage and of the bone. Numerous experimental investigations indicate that TNF $\alpha$  (tumor necrosis factor  $\alpha$ ) plays a central role in the development of degenerative joint diseases. Osteoarthrosis is always associated with the destruction of cartilage and bone. In the case of osteoarthrosis, neutrophil granulocytes, which release TNF $\alpha$ , migrate increasingly into the joint. Furthermore, under the influence of TNF $\alpha$ , there is increased formation of new vessels. Consequently, the growth of cartilage and bone-damaging tissue is promoted (Paleolog, E. Target effector role of vascular endothelium in the inflammatory response: insights from the clinical trial of anti-TNF $\alpha$  antibody in rheumatoid arthritis. *Mol. Pathol.* 50, 225 - 233, 1997). It has been tested unambiguously in clinical studies that the neutralization of TNF $\alpha$ , either by monoclonal antibodies (anti-TNF mABs), directed against TNF $\alpha$ , or through the use of soluble TNF $\alpha$  receptors (soluble TNF receptor fusion proteins: sTNFR-IgGs), not only the acute symptoms (such as joint swelling) but also the steadily progressing cartilage and bone destruction can be suppressed (Fenner, H. Immunopharmacological Profile and Therapeutic Perspectives of Anti-TNF $\alpha$  Therapies, *Zeitschrift. Rheumatol.* 57, 294 - 297, 1998; Moreland, L.W., Soluble tumor necrosis factor receptor (p75) fusion protein (Enbrel) as a therapy for rheumatoid arthritis. *Rheum Dis. Clin. N.A.* 24, 579 - 591, 1998). Accordingly, it is entirely conceivable that, by

using anti-TNF mABs and sTNFR-IgGs, the formation of the destructive cartilage and bone changes could be prevented.

Predominantly NSAIDs are prescribed in veterinary medicine for the treatment of chronic pain. At the present time, especially the following active materials are used: aspirin, carprofen, ketoprofen, piroxicam, naproxen and meclofenamic (Papich, G.M., Hardie E.M., Management of chronic pain). There are numerous references to the fact that nonsteroidal anti-inflammatory drugs are able to alleviate pain but, if anything, promote cartilage destruction (Wang, B, Yao, Y-Y, Chen M-Z. Effects of indomethacin on joint damage in rat and rabbit. Acta Pharmacol. Sinica 19, 70 - 73, 1998; Rainsford, KD, Ying, C, Smith FC., Effects of meloxicam, compared with other NSAIDs, on cartilage proteoglycan metabolism, synovial prostaglandin Es, and production of interleukins 1, 6 and 8, in human and porcine explants in organ culture. J. Pharm. Pharmacol. 49, 991 - 998, 1997; van der Berg, WB. Impact of NSAID and steroids on cartilage destruction in murine antigen induced arthritis, J. Rheumatol. 27 (Suppl.), 122 - 123, 1991; Brandt, KD, Slowman-Kovacs, S. Nonsteroidal anti-inflammatory drugs in treatment of osteoarthritis. Clin. Orthopaed. Relat. Dis. 213, 84 - 91, 1986; Palmowski, MJ, KD Brandt. Aspirin aggravates the degeneration of canine joint cartilage caused by immobilization. Arthritis Rheum. 25, 1333 - 1342, 1982).

As is well known, NSAIDs, as inhibitors of cyclooxygenase and by shifting the arachidonic acid metabolism, bring about a reproduction of leukotrienes, which are capable of promoting the degenerative processes (Brune, K, Aehringhaus, U, Peskar, B.A., Pharmacological control of leukotriene and prostaglandin production from mouse peritoneal macrophages, Agents Actions 14, 729 - 34, 1984; Achterrath-Tuckermann, U., Th. Simmet, W. Luck, I. Szelenyi, B.A. Peskar. Inhibition of cysteinyl-leukotriene production by azelastine and its biological significance. Agents Actions 24, 217 - 223, 1988).

Furthermore, NSAIDs are associated with serious gastrointestinal and other side effects, which are life-threatening under some circumstances (Forsyth, SF, Guilford, WG, Haslett, SJ, Godfrey, J., Endoscopy of the gastroduodenal mucosa after carprofen, meloxicam and ketoprofen administration in dogs. J. Small Animal Practice 39, 421 - 424, 1998).

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In recent years, two sub-types of cyclooxygenases (COX) were discovered, COX-1 and COX-2. The COX-1 enzyme is a so-called "housekeeping" enzyme, one of the tasks of which is to protect the gastrointestinal mucosa as well as to take care of maintaining the necessary renal blood supply and to maintain adequate blood circulation. On the other hand, the COX-2 enzyme is induced by various factors and is responsible for inflammatory processes. Since none of the previously known NSAIDs has a therapeutically relevant selectivity for COX-2 and, instead, inhibit both enzymes almost equally, it is no wonder that gastrointestinal side effects occur also with the NSAIDs introduced recently. Selective COX-2 inhibitors, which do not inhibit the so-called "housekeeping" enzyme COX-1 and, with that, the prostaglandin synthesis in the gastrointestinal tract, do not lead to gastrointestinal damage. NSAIDs, such as acetylsalicylic acid, ibuprofen, ketoprofen, naproxen, carprofen, diclofenac, meclofenamic acid, piroxicam and meloxicam, however, are not selective COX-2 inhibitors.

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According to some investigations, meloxicam is said selectively to inhibit COX-2 (Churchill, L, AG Graham, CK Shih. Selective inhibition of human cyclooxygenase-2 by meloxicam. Inflammopharmacol. 4, 125 - 135, 1996). However, clinical results contradict this selectivity, since typical NSAID-induced incompatibility reactions, such as gastrointestinal and renal disorders occur when meloxicam is used (Committee on Safety of Medicine/Medicines Control Agency. Meloxicam (Mobic): gastrointestinal and skin reactions. Current Problems 24, 13, 1998; Gaâner, G, I Stephan, I Schütt-Mast. Observations concerning the side effects after using nonsteroidal anti-inflammatory drugs in dogs. Tierärztl. Prax. 26(K), 119 - 123, 1998).



Other NSAIDs, such as carprofen, inhibit the two subtypes of COX with equal intensity (Vane, JR, RM Botting. New insights into the mode of action of anti-inflammatory drugs. *Inflamm. Res.* 44, 1 - 10, 1995). Accordingly, when such NSAIDs are used, gastrointestinal side effects can occur (Forsyth, SF, WG Guilford, SJ Haslett, J Godfrey. Endoscopy of the gastroduodenal mucosa after carprofen, meloxicam and ketoprofen administration in dogs. *J. Small Animal Pract.* 39, 421 - 424, 1998; Tjalve, H., Adverse reactions to veterinary drugs reported in Sweden during 1991 - 1995. *J. Vet. Pharmacol. Therap.* 20, 105 - 110, 1997).

In the case of carprofen, it was necessary to change the information regarding side effects insofar as it was necessary to indicate also possible gastrointestinal incompatibilities (bleeding, formation of ulcers). Possible impairment of the renal function, which is a typical side effect of NSAIDs, had to be mentioned in the new package insert for carprofen (Veterinary reporting results in product labeling change, USP Quality Review No. 63, May 1998).

Aside from the classical, gastrointestinal and renal side effects, many analgesics may also cause other undesirable reactions, which cannot be explained by the inhibition of the COX enzyme. They are substance specific and occur with certain medicinal drugs.

For example, in the case of diclofenac, naproxen, nimesuli and piroxicam, liver damage has occasionally been observed (Helfgott SM, et al., Diclofenac-associated hepatotoxicity. *JAMA* 264, 2660 - 2662, 1990; Andrejak, M, et al., Cross hepatotoxicity between nonsteroidal anti-inflammatory drugs. *Br. Med. J.* 295, 180 - 181, 1987; McCormick, PA, et al., COX-2 inhibitor and fulminant hepatic failure, *Lancet* 353, 40 - 41, 1990; Paterson D, et al., Piroxicam induced submassive necrosis of the liver. *Gut* 33, 1456 - 1458, 1992).

Heptatotoxicity has also been reported for the arylpropionic acid, carprofen, for

which it was also possible to prove the causality, since in most dogs, complete normalization of the liver values occurred when the carprofen treatment was discontinued (MacPhail, CM, MR Lappin, DJ Meyer, SG Smith, CRL Webster, PJ Armstrong. Hepatocellular toxicosis associated with administration of carprofen in 21 dogs. JVMA 212, 1895 - 1901, 1998).

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As a result of this finding, it was also necessary to take up this not-COX-specific side effect in the new package inserts for carprofen (Veterinary reporting results in product labeling change, USP Quality Review No. 63, May 1998).

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Many NSAIDs are racemic mixtures. With the exception of naproxen, all arylpropionic acid derivatives are such mixtures. This means that the R as well as the S isomer is present in commercially obtainable formulations. However, only the S isomers are pharmacologically and therapeutically effective. However, both isomers are metabolized in the organism and both isomers have to be eliminated from the body. The additional metabolism and elimination of the pharmacodynamically inactive isomer represents an appreciable burden for the organism. If racemic mixtures are used therapeutically, the organism is burdened with 50% of ballast materials. Furthermore, under some circumstances, the inactive isomers can also contribute to drug interactions (Szelenyi, I, G Geisslinger, E Polymeropoulos, W Paul, M Herbst, K Brune. The real Gordian knot: Racemic mixtures versus pure enantiomers. Drug News & Perspectives 11, 139 - 160, 1998).

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It is also known that NSAIDs, such as diclofenac and aspirin, are tolerated incomparably better in human therapy than in dogs. Investigations have shown that treatments of dogs with diclofenac had to be terminated because of malaise and vomiting (Wigger, et al., Plasma and tissue kinetics of diclofenac in the dog. Arch. Pharmacol. 357; No. 4, Suppl; R5, 1998).

The importance of the treatment of pain as well as of the prevention of the development of chronic pain in the case of degenerative joint diseases in dogs and cats is constantly increasing. Aside from a good analgesic effectiveness of the material used, especially the potential for developing side effects must be small here.

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It must be easy to administer the appropriate pharmaceutical preparations to dogs and cats and the preparations must be available in a pleasant tasting, readily tolerated form.

#### Description of the invention

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The invention relates to a process for ameliorating and preventing inflammatory chronic pain from a degenerative joint disease in household pets as dogs and cats, in which there is administered to a household pet in need therefor a dosage of an analgesically effective amount of flupirtine or a pharmaceutically acceptable salt of flupirtine, optionally together with one or more active ingredients that is an antiinflammatory, an analgesic other than flupirtine, a steroid, a

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chondroprotector, a TNF $\alpha$  receptor, and a plant extract.

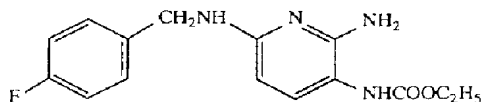
It was surprisingly found that flupirtine or its pharmaceutically acceptable and tolerated salts can be used for the treatment of pain as well as for preventing chronic pain developing in the case of degenerative joint diseases in household pets such as dogs and cats and that it has a low potential for developing side effects. Flupirtine has previously not been known

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to be used in veterinary medicine.

Flupirtine is a triaminopyridine derivative and has the chemical name 2-amino-6-[[[(4fluorophenyl)methyl]amino]-3-pyridinyl]carbonic acid ethylester, with the formula

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Flupirtine is an analgesic, which acts on the central nervous system. It is not addictive and does not produce the side effects, such as constipation, respiratory depression, development of tolerance and withdrawal symptoms, which are typical of other analgesics that act on the central nervous system. It is known from the literature, that flupirtine can be used in human therapy for the treatment of different diseases. For example, flupirtine has muscle relaxing properties, so that it can also be used for the treatment of muscle spasms or for diseases, which are based on muscle spasms (e.g. German patent No. 4,022,442, and US patents Nos. 5,162,346; 5,284,861).

Moreover, during investigations of the muscle relaxing action of flupirtine in rats, it was found that flupirtine is also suitable for the treatment of NMDA-induced CNS diseases, such as cerebral ischemia, neurodegenerative diseases and epilepsy (German patent No. 4,327,516, and US patent No. 5,721,258). In international publication WO 97/170/072, the use of flupirtine was indicated for the treatment of diseases of the hematopoietic cell system, such as AIDS.

Likewise, it was possible to show that flupirtine can be used for the treatment of diseases, which are associated with an unphysiologically high cell mortality rate (international patent publication WO 97/49398).

The synthesis of flupirtine and its pharmaceutically usable salts is described in German patents Nos. 1,795,858; 3,133,519; and 3,416,609.

With regard to the mechanism of action of flupirtine, there are several mechanisms, which explain its analgesic effect: (1) Flupirtine activates the noradrenergic descending paths in the spinal cord (Nickel, B., Engel, J., Szelenyi, I., Possible involvement of noradrenergic descending pain-modulation pathways in the mode of antinociceptive action of flupirtine, a novel,

non-opioid analgesic. Agents Actions 23, 112 – 116, 1988; Szelenyi, I., Nickel, B., Bore, HO., Brune, K., Mode of action of flupirtine in the rat. Br. J. Pharmacol. 97, 835 – 842, 1989); (2) Flupirtine intensifies the antinociceptive GABAergic mechanisms (Weiser, T., Wienrich, M., Szelenyi, I., The amplification of the GABA<sub>A</sub> response by flupirtine is mediated via the steroid binding site. Arch. Pharmacol. 349 (Suppl.) R 383, (1994); (3) There are numerous references in the literature to the fact that opening the ATP-sensitive K<sup>+</sup> channels leads to an analgesic effect (Asano, T., Iida, H., Dohi, S., Masue, T., Shimonaka, H., Nicorandil, as ATP-sensitive K<sup>+</sup> channel opener, potentiated morphine analgesia. Jap. J. Anesth. 45, 1342 – 1346, 1996; Robles, LI., Barrios, M., Del Poza, E., Dordal, A., Baeyens, JM. Effects of K<sup>+</sup> channel blockers and openers on antinociception induced by agonists of 5-HTA receptors, Eur. J. Pharmacol. 295 181 – 188, 1996). Our own investigations indicate that the active ingredient, flupirtine, opens up certain K<sup>+</sup> channels and develops its analgesic effect over this path; and (4) According to the most recent investigations, flupirtine also opens up the so-called stress-independent K<sup>+</sup> channels in the central nervous system. On the basis of this mechanism of action, flupirtine is also able to prevent the development of chronic pain (Kornhuber, J., A pain medication, which differs from all known analgesics. Med. Woche 64, 10 (1999).

It is most probable that the analgesic action of flupirtine comes about due to a combination of the effects named above. For example, it was shown that that the opening of the central ATP-dependent K<sup>+</sup> channels not only per se has antinociceptive activity, but that it also activates the noradrenergic descending pain-modulated paths in the spinal cord (Narita, M., Takamori, K., Kawaschima, N., Funada, M., Kamei, J., Suzuki, T., Misawa, M., Nagase, H., Activation of central ATP-sensitive potassium channels produces the antinociception and spinal noradrenaline turnover-enhancing effect in mice. Psychopharmacol. 113, 11 – 14 (1993).

The mode of action of flupirtine thus clearly differs from that of the so-called peripheral analgesics, such as aspirin, ibuprofen and diclofenac, which develop their analgesic

action by inhibiting the cyclooxygenase. Since the prostaglandin synthesis is not inhibited by flupirtine, there is also no damage to the gastrointestinal mucosa. The renal function is also not affected by flupirtine. No indications of a liver-damaging effect were found in chronic, toxicological investigations ( 6 – 12 months).

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The analgesic effect of flupirtine was experimentally investigated on conscious dogs. A silver wire was inserted and fixed under anesthesia in the dental pulp of the animals (second molar tooth). Subsequently, the animals were trained to become accustomed to the personnel. One week after the silver wire was implanted, the animals were included  
10 in the experiment. The silver wire was connected to a pulse generator, with the help of which the intensity of the current could be infinitely regulated. Flupirtine was administered orally in a capsule to the dogs. After 30 minutes, the intensity of the current was increased at a continuous rate. At the first signs of a sensation of pain, the current generator was switched off immediately. The intensity of the current at the first signs of pain was observed and taken as the pain threshold.  
15 Symptoms, such as salivation, licking the lips, twitching of the face muscles were regarded as indications of pain. When flupirtine was intravenously administered, the measurement of the pain threshold was made after 10 minutes.

The results are summarized in Table 1.

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**Table 1**

Substances	ID <sub>50</sub> in mg/kg orally	ID <sub>50</sub> in mg/kg intravenously
Flupirtine	3.5	0.7
Ibuprofen	18	-
Diclofenac	7.8	-
Buprenorphin	1.2	0.08

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Flupirtine is clearly superior in dogs to ibuprofen as well as to diclofenac with  
30 regard to the analgesic strength of action. Buprenorphin is a very effective analgesic with a very

low oral bioavailability and belongs to the classic morphine derivatives. It is therefore not surprising that the analgesic effect of buprenorphin, after intravenous administration, is appreciably stronger than that of flupirtine. However, after oral administration the analgesic effect of flupirtine is comparable to that of buprenorphin.

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It can be noted in summary that flupirtine has a very strong analgesic potential in dogs. Because of the mechanism of action and of the toxicological results obtained, gastrointestinal, renal or hepatic damage is not expected from acute or long-term use.

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Flupirtine can be administered preferably orally, parenterally or rectally for the treatment of pain resulting from degenerative diseases in dogs and cats. Suitable forms of administration are granulates, pellets, capsules, micro-capsules, coated pills, film-coated tablets, chewable tablets, sustained release tablets, two-layer tablets, sustained release capsules, big pills, suppositories or injection solutions.

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In this connection, tablet formulations with a single or a double breaking notch may be advantageous here, in order to improve the administration of the individually required amount to the animals.

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To increase the acceptance of the oral form of administration for dogs and cats, can further include one or more taste improvers as Trigarol Digest P (sold by Haarmann & Reimer GmbH) or artificial meat flavors, such as those consisting of a vegetable protein and soybean oil and dried pigs liver powder, can be added suitably in amounts of from about 5 to about 10% to the tablet granulate.

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For oral forms of administration, the single dose of flupirtine maleate can be suitably from about 0.1 to about 20 mg/kg and more suitably from about 1 to about 5 mg/kg.

Capsules containing 100 mg flupirtine maleate can be administered from about 2 to about 3 times daily. The maximum daily dose should suitably not exceed about 600 mg.

Suppositories, as a single dose, can contain from about 0.1 to about 30 mg/kg and suitably from about 2.5 to about 7.5 mg/kg of flupirtine maleate. For example, suppositories with a dosage of 100 to 300 mg of flupirtine maleate can be administered from about 2 or about 3 times daily. The maximum daily dose should suitably not exceed about 900 mg.

Parenteral forms of administration, suitable injection solutions for intra-muscular application, can contain from about 1.5 to about 5 mg/kg of flupirtine gluconate, because it is locally better tolerated. For example, ampules with 164.5 mg of flupirtine gluconate in 3 ml solution can be administered once daily.

#### Examples

##### Flupirtine Tablets Scored Twice

2-Amino-3-carbethoxyamino-6-(4-fluoro-benzylamino)-pyridine maleate (10 kg) is granulated with 2.5 kg of calcium hydrogen phosphate and 2.5 kg cornstarch, and the mixture is granulated with a solution of 1 kg polyvinylpyrrolidone in 4 kg demineralized water by a procedure known *per se*. After 1.3 kg cornstarch, 2 kg microcrystalline cellulose, 0.6 kg magnesium stearate and 0.1 kg highly disperse silica, as well as 1.5 mg the taste-improver, Trigarol Digest P, are added, 200mg double-scored tablets are pressed, having a diameter of 9 mm and a radius of curvature of 10 mm.

The breaking strength of the tablets is 80 N to 100 N (Schleuniger Breaking Strength Tester). The disintegration time, measured according to DAB 8, is 5 minutes. Each tablet contains 100 mg of active ingredient.



## Flupirtine Capsules

A capsule filling is prepared by a method similar to that described above for tablets and filled into hard gelatin capsules of a suitable size in an amount of 200 mg per capsule. One capsule contains 100 mg of active ingredient.

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## Flupirtine Injection Solution

The following manufacturing process described is for a batch of 20 ℓ (for 6,500 ampules. Water (10.0 ℓ) is heated to 70°C, 1562.0 g gluconic acid delta lactone is added and the solution is kept for 1 hour at 70°C. At the same time, nitrogen is passed through the solution.

10 Polyethylene glycol (8000.0 g), with a molecular weight of 380 to 420, is weighed into the solution, which is then heated under nitrogen to 70°C. A second solution is prepared from disodium sulfite (30.0 g) by dissolving it in 500.0 ml water under nitrogen. Flupirtine base (666.6 g) is screened through a sieve with a mesh width of 0.3 mm and dissolved in the second solution through which nitrogen is intensively passed. The second solution is cooled and diluted to 20 ℓ

15 with water, while passing nitrogen therethrough. The solutions are combined and the resulting solutions are sterilized by filtering it through a membrane filter, with a pore width of 0.2 μm and a preliminary fiberglass filter. In-process control is carried out by measurement of the oxygen content of the solution by an oxygen electrode, and the pH of the solution is measured.

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The resulting solution is filled in 3 ml amounts under aseptic conditions and under a blanket of nitrogen into colorless ampules. One ampule contains 164.5 mg flupirtine gluconate in 3 ml of solution.

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In accordance with the present invention, flupirtine or its pharmaceutically acceptable salts can also be used in combination with other active ingredients for the treatment of pain in the case of degenerative joint diseases in dogs and cats.

For this purpose, the following combinations of one or more ingredients can be advantageously used:

Flupirtine in combination with inflammation inhibitors, especially with one or more of selective COX-2 inhibitors, such as celecoxib, rofecoxib, valdecoxib and parecoxib to intensify the effect;

Flupirtine, in combination with other analgesics, which act on the central nervous system, such as one or more of nefopam, tramadol, nalbuphin, dextropropoxyphen;

Flupirtine in combination with metamizol;

Flupirtine in combination with one or more of chloroquin, hydroxychloroquin, methotrexate, penicillamine, ademetionine, sulfasalazine, beta-sitosterol, thiamine, cyanocobalamine, pyridoxine;

Flupirtine in combination with one or more steroids, such as prednisolone, methylprednisolone;

Flupirtine in combination with one or more chondroprotective substances, such as chondroitin, glucosamine and polysulfated glycosaminoglycan;

Flupirtine in combination with one or more TNF $\alpha$  receptors; and

Flupirtine in combination with one or more plant extracts, such as rampion root, nettle leaves, pockwood tree wood, willow bark, arnica.

The suitable dosage form of flupirtine, or its dosage form in combination with other active ingredients, suitably also contains one or more of one or more pharmaceutical carrier and one or more pharmaceutical auxiliary ingredient.

We claim:

1           1. A process for ameliorating and preventing inflammatory chronic pain from a  
2           degenerative joint disease in household pets, which comprises administering to a household  
3           pet in need therefor a dosage of an analgesically effective amount of flupirtine or a pharma-  
4           ceutically acceptable salt thereof, optionally together with one or more active ingredients of  
5           an antiinflammatory, an analgesic other than flupirtine, a steroid, a chondroprotector, a  
6           TNF $\alpha$  receptor, and a plant extract.

1           2. The process of claim 1, wherein among said optional one or more ingredi-  
2           ents the antiinflammatory is one or more of selective COX-2 inhibitors.

1           3. The process of claim 2, wherein said one or more COX-2 inhibitors is one  
2           or more of celecoxib, rofecoxib, valdecoxib, and parecoxib; said analgesic other than  
3           flupirtine is one or more of nefopam, tramadol, nalbuphin, and dextropropoxyphen; said  
4           steroid is one or more of prednisolone, and methylprednisolone; said chondroprotector is  
5           one or more of chondroitin, glucosamine, and polysulfated glycosaminoglycan; said plant  
6           extract is one or more of rampion root, nettle leaf, pockwood tree wood, willow bark, and  
7           arnica; and optionally one or more of metamizol, chloroquin, hydroxychloroquin,  
8           methotrexate, penicillamine, ademetionine, sulfasalazine,  $\beta$ -sitosterol, thiamine,  
9           cyanocobolamine, and pyridoxine.

1           4. The process of claim 3, wherein said household pet is a dog or a cat.

1           5. The process of claim 1, wherein the pain to be ameliorated or prevented is  
2           caused by one or more of hip joint displasia, kneecap luxation, dachshund paralysis, Cauda-  
3           equina syndrome, in a dog or a cat.

1           6. The process of claim 1, wherein said flupirtine or its pharmaceutically  
2 acceptable salt, or its optional combination with an active ingredient, further comprises one  
3 or more of one or more pharmaceutical carrier, and one or more of a pharmaceutical  
4 auxiliary ingredient.

1           7. The process of claim 1, wherein said dosage further comprises a taste  
2 improver.

1           8. The process of claim 3, wherein said dosage further comprises one or more  
2 additive of Trigarol Digest P, an artificial meat flavoring, a vegetable protein, soybean oil,  
3 and dried pig liver powder.

1           9. The process of claim 8, wherein said additive is present in a concentration of  
2 from about 5 to about 10% based on the dosage.

1           10. The process of claim 1, wherein said dosage is a granulate, tablet, capsule,  
2 large pill, powder, suppository, or injection.

1           11. The process of claim 1, wherein said dosage is a film-coated tablet, a  
2 chewable tablet, a 2-layer tablet, or a sustained release tablet, all with or without a  
3 breakable scoring.